

Successful Treatment of Epidermolysis Bullosa Pruriginosa with Anti-IgE Therapy (Omalizumab): A Case Report and Four Years Follow Up

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ABSTRACT

Importance: Epidermolysis bullosa pruriginosa (EBP) is a rare adult-onset heredo-familial skin disorder. Bullous skin lesions are triggered by intense pruritus, which is the hallmark of the disease. Eosinophilic infiltrates and elevated IgE levels in serum and lesions have been reported, but their pathological role is yet to be determined. Although treatment with anti-IgE therapy (Omalizumab) has been used successfully in autoimmune bullous diseases but not in EBP to our knowledge.

Observation: We report a case of a 34-year-old female with adult-onset pruritic and blistering disease of the skin. Sub epidermal blisters with viable roofs and numerous epidermal neutrophils and eosinophilic infiltrate were detected histopathologically; however, the absence of IgA, IgG, IgM, C1q, and C3 deposits made the diagnosis of Epidermolysis bullosa acquisita and Bullous pemphigoid uncertain. Whilst testing for intra-lesional IgE autoantibodies was not performed, total and specific serum IgE concentrations increased during her illness in the absence of an allergic or parasitic disease. Because no improvement in her symptoms was observed with conventional treatments, whole exome sequencing was performed which showed a non-conservative Glycine substitution in the G2481D residue in the COL7A1 gene suggestive of EBP. Off-label use of anti-IgE drug (Omalizumab) was attempted due to severity of her symptoms and elevated levels of IgE. On initiating the treatment, the patient showed a significant improvement in her skin condition; however, a trial to taper off Omalizumab two years later was unsuccessful.

Conclusion: This case suggests a possible role of IgE autoantibodies in EBP that requires further research, consolidated by the fact that our patient showed improvement with anti-IgE therapy. Furthermore anti-IgE therapy offers a possible new targeted treatment for EBP in the absence of curative treatments.

Keywords: Autoimmune bullous disease; Dystrophic epidermolysis bullosa; Epidermolysis bullosa pruriginosa; IgE autoimmunity; Omalizumab

INTRODUCTION

Dystrophic epidermolysis bullosa (DEB) is caused by point genetic mutations in the COL7A1 gene, which encodes the anchoring fibrils of the basement membrane to the underlying dermis; this mutation causes skin fragility and renders it more susceptible to friction [1].

Epidermolysis bullosa pruriginosa (EBP) (OMIM #604129) is one of DEB rare clinical phenotypes. Intractable pruritus and prurigo-like lichenified nodules are cardinal features of the adult disease form. Pruritus, usually precedes or co-exists with the severe clinical phenotype [2]. Identical COL7A1 gene mutations could cause DEB or EBP clinical phenotype [3], which suggests an additional unknown immunological or environmental mechanism. Rarity of the disease, a variable age of onset and

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clinico-histological resemblance to other skin conditions makes the diagnosis challenging [4]. Treatment options are limited to a few medications with a high side effect burden making the treatment of pruritus even more difficult [5].

CASE REPRESENTATION

A 34-year-old woman presented to the dermatology clinic with a one-year history of pruritic bullous lesions after minor trauma to the skin. She had a past history of a resected thyroid papillary carcinoma and no childhood atopic disease. Her aunt and a maternal cousin also had bullous skin lesions. On examination, Lichenoid papules were noted with a few vesicles, along with blisters on extensor surfaces of upper and lower limbs, sparing nail, scalp, and mucous membranes (Figure 1). A punch skin biopsy revealed subepidermal blister with a viable roof, epidermal and upper dermal oedema, and perivascular lymphocytic, neutrophilic, and eosinophilic infiltrates. Immunofluorescent assays for IgA, IgG, IgM, C1q, and C3 as well as serum epidermal IgG, celiac disease antibodies, and autoimmune workups were negative. Systemic glucocorticoids at a concentration of 0.5 mg/kg, along with cyclosporine and dapsone, failed to control her symptoms. Repeated skin biopsies were inconclusive. Serum total IgE increased to 2587 ku/l (357 ku/l at baseline). Specific IgE titers for the dermatophagoids *pteronyssinus* and *farinae* were 2.23 Ku/L and 5.08Ku/L, respectively. Whole exome sequencing (XomeDxPlus- NY, USA) showed a G2481D variant homozygous, non-conservative amino acid substitution mutation in the COL7A1 gene. This variant has not been identified in the literature as a pathogenic or benign polymorphism; however, in silico analysis predicted a protein-damaging role. As her parent's DNA samples were not analyzed, a novel mutation could not be confirmed.



Figure 1: Epidermolysis bullosa pruriginosa skin lesions (Lichenoid papules with few vesicles and sloughed bullae seen on the patient's lower limbs).

Omalizumab (anti-IgE) was administered in 300 mg subcutaneous injections every four weeks, resulting in a

dramatic improvement in pruritus and bullae. Resolution of symptoms was maintained for four years and attempts to stop Omalizumab caused disease relapse.

DISCUSSION

Self-antigens instigating IgE-mediated autoimmune diseases were recently described [5]. Bullous Pemphigoid (BP) was among the first of the autoimmune skin diseases demonstrating IgE's self-reactive role. The presence of auto-reactive IgE-antibodies against transmembrane protein BP180 and intracellular protein BP230 and IgE-coated mast cells in perilesional skin with BP180 peptides on these mast cells [6] support the involvement of IgE autoantibodies in the pathogenesis of BP.

Increased concentrations of serum and intra-lesion IgE were repeatedly observed in EBP cases [2,7,8], however a link to disease pathogenicity has not been established yet. Severe itching, which is central to a diagnosis of EBP, in the context of increased IgE suggests a causative role of IgE, particularly when skin lesions are provoked or increased by pruritus. Histamine which is a well-known pruritogen is released primarily by mast cells, when an allergen binds to the IgE receptor on their surface [9]. Auto-reactive IgE have recently been identified in Epidermolysis bullosa acquisita, which was previously viewed as a disorder reminiscent of Dystrophic epidermolysis bullosa (DEB) [10]. Similarly in EBP, autoimmune IgE could be the potential culprit triggering the inflammatory cascade in those who are genetically susceptible.

Omalizumab blocks free serum IgE from binding to the high-affinity FcεRI on mast cells. It has been licensed for treatment of chronic spontaneous urticaria (CSU) and postulated mechanisms include reducing the activity of IgG autoantibodies against FcεRI, reducing the activity of auto-reactive IgE against unknown antigens and reducing intrinsically abnormal IgE [11]. Omalizumab has been used to treat BP successfully in the past [12]. Despite this, no data is available on the effects of Omalizumab in the treatment of EBP.

CONCLUSION

The current case is the first in our knowledge, to be genetically confirmed as EBP and successfully treated with Omalizumab. The diagnosis of EBP was initially challenging due to the late-onset presentation and lack of other supporting features like nail dystrophy. The improvement in bullous skin lesions and disabling pruritus after Omalizumab treatment further supports the etio-pathological role of IgE. In patients with EBP, increased serum IgE in the absence of obvious allergic or parasitic disease may support the use of anti-IgE therapy when conventional therapy fails.

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CONFLICT OF INTEREST

Author and coauthors have no financial disclosures to declare.

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